ONLINE COURSE REPORT on

INTRODUCTION TO SYSTEMATIC REVIEW AND META-ANALTYSIS

By

Dr. KUNCHALA SAI SWAPNIKA

MBA-hospital and health management

(2019-2021)

INTRODUCTION

"Introduction to systematic review and meta analysis" is an online course of 35 hours of teaching from Coursera platform provided by John Hopkins University. **Systematic reviews** are a type of literature review that uses systematic methods to collect secondary data, critically appraise research studies, and synthesize findings qualitatively or quantitatively. Systematic reviews may examine clinical tests, public health interventions, environmental interventions, social interventions, adverse effects, and economic evaluations. **Meta-analysis** is the statistical procedure for combining data from multiple studies. When the treatment effect (or effect size) is consistent from one study to the next, **meta-analysis** can be used to identify this common effect

COURSE DESCRIPTION

The methods to perform systematic reviews and meta-analysis of clinical trials are introduced in the course. Also, the process of how to formulate an answerable research question, defining inclusion and exclusion criteria, searching for the evidence, extracting data, assessing the risk of bias in clinical trials, and performing a Meta Analysis are covered.

OBJECTIVES

- Learn the steps that comprise systematic review and meta analysis
- To be able to read and understand the literature related to systematic review and meta analysis in future
- Be able to integrate the results of systematic reviews into the work

COURSE CONTENTS

- Introduction to systematic review and meta analysis
- Framing the question
- Finding the evidence- searching principles
- Assessing the risk of bias in clinical trials

- Minimizing bias
- Qualitative synthesis and interpreting results
- Planning the Meta analysis
- Statistical methods for meta analysis

Definition of systematic review

It focuses on specific question. It uses explicit methods to Identify, select, appraise and synthesize results from similar but separate studies. All systematic reviews are not meta analysis . Systematic reviews formulate research questions that are broad or narrow in scope, and identify and synthesize studies that directly relate to the systematic review question. They are designed to provide a complete, exhaustive summary of current evidence, published and unpublished, that is "methodical, comprehensive, transparent, and replicable

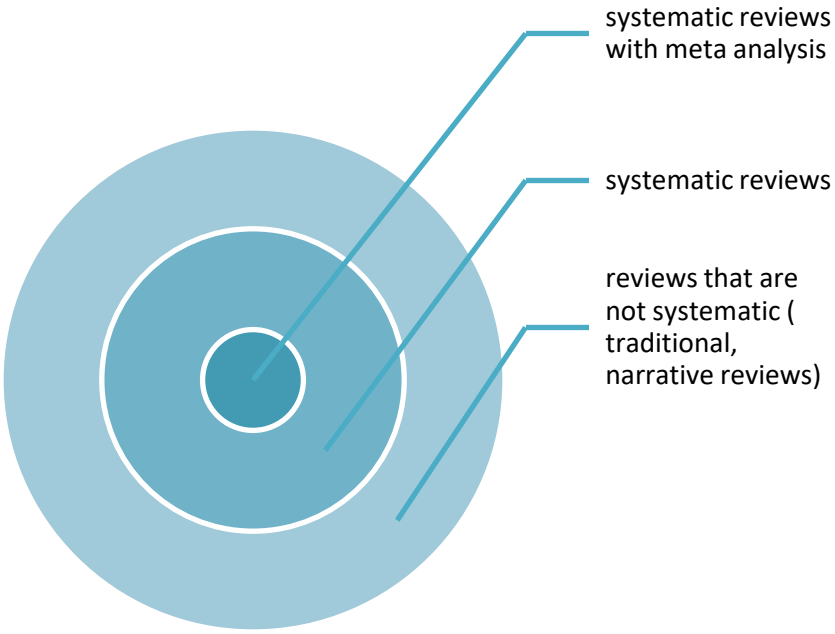
Definition of meta analysis:

Meta Analysis is the statistical analysis which combines the results of several independent studies considered by the analyst to be combinable. It is an optional component of systematic review.

- It can help to assess the strength of evidence
- To combine results quantitatively
- Investigate Heterogeneity

When to do a Meta Analysis:

- When more than one study has estimated a treatment effect of association
- When the difference in te study characteristics are unlikely to effect the treatment effect
- When the treatment effect have been measured and reported in similar ways



FEATURES OF SYSTEMATIC REVIEW:

- Facilitate efficient integration of information for rational decision making
- Provides clear and transparent process
- Demonstrates where the effects the healthcare are considered and where they vary
- Minimize bias and reduce change effects
- Meta analysis can proceed more precise estimates than individual studies
- Can be readily updates as needed
- Allows decisions based on the totality of the available evidence

who use systematic reviews : individual doctors, researchers, policy makers (regulatory authorities, purchasers etc)

levels of evidence:

STEPS IN CONDUCTING A SYSTEMATIC REVIEW

- Frame research question (PICO/PICOS)
- Develop search strategy
- Develop protocol
- Run search strategy in at least two databases
- Retrieve and duplicate citations
- Develop system for screening titles / abstracts and full texts
- Retrieve and screen full texts
- Develop forms for assessing 'risk of bias' and extracting data
- Clean and manage data
- Conduct qualitative synthesis
- Conduct meta analysis (if appropriate)
- Write report of systematic review
- Update systematic review

FRAMING RESEARCH QUESTION

Elements of the question:

While framing the question we should consider

- consider patients/interventions/outcome/comparison
- Classify type of question
- Identify application of study designs to address questions
- Find the evidence
- Critically appraise and apply evidence

Components of well constructed and answerable questions (clinical)- PICO framework

P – population/patients

Types of P : define condition/disease, including explicit diagnostic criteria

Population and setting of interest (Age, sex, race, community, hospital , OP)

I – intervention/exposure

Types of risk factors, exposure, interventions (I): timing of exposure , route of examination, dose intensity , duration of exposure or therapy

C – comparison groups

Types of comparison groups (C): for trials- placebo , standard therapy , no treatment

For experiment – no exposure, non cases hospitals, neighborhood)

0 – outcome

Types of outcomes (O) : criteria for defining , important to consumers and producers , unpublished data

PICO Vs PICOTS:

T- Timing (duration of minimum follow up)

S – Setting (primary care, specialty, inpatients)

Example of framing a question:

1) is drug therapy associated with long-term morbidity and mortality in older persons with moderate hypertension

   P – Older persons with moderate hypertension

   I – drug therapy

   C – Not mentioned

   0 – long-term morbidity and mortality

Analytical framework for systematic review

Components: specifies PICO,T,S

Identifies potential modifiers and mediators of efficiency

Clarifies links between intermediate and health outcomes

Finding evidence

SEARCHING PRINCIPLES:

Identifying key sources for data-

- key electronic databases
- controlled vocabulary (indexing)
- indexing of RCT and observational studies
- other sources: (trial registers, gray literature searching, personal contacts)

KEY ELECTRONIC DATABASES:

Major bibliographic databases for RCTs and observational studies: Medline/pub med, EMBASE, COCHRANE central registar of controlledtrials, national and regional databases (LILACS0), subject specific databases (CINAHL, psychINFO, OTseeker)

Other databases: citation databases (web of science, Scopus(dissertations, thesis bases), gray literature databases)

CONTROLLED VOCABULARY-

Consistency: alternative spellings, synonyms, plurals, related items

Finding evidence: Pub med/Medline

Searching for studies in Pub med:

- medical subject heading (MeSH)
  . description(thesaurus)
  .most specific term used
- publication type
- keywords used(titles since 1966, abstracts since 1975, truncation useful)

EMBASE: European Medline, more than 7000 periodicals, nineteen million records

- advanced search is used to map and explore preferred terms along with synonyms

CENTRAL : includes each COCHRANE review groups trials register

- includes all hand searched results
- includes RCTs and controlled trials from MEDLINE and EMBASE
- easy, reliable access to maximum number of trials
- searchable with MeSH terms

ISI web of science: multidisciplinary research databases, including citation from sciences(1900), social sciences(1956) and arts and humanities(1956)

- strength in citation mapping
- no controlled vocabulary

Systematic snowballing: uses included articles as a source to identify missing studies

- reference lists
- web of science, SCOPUS
- "related articles"/"find similar" in MEDLINE and EMBASE

HAND SEARCHING:

Journals in topic area, conference proceedings: biosis, bibliographies of systematic reviews or individual studies, gray literature (dissertations, industry files or open reports)

BUILDING HIGH QUALITY SEARCH STRATEGY:

For example, consider development of Medline search strategy,

- Start with simple search strategy
- Run search and retrieve reports
- Analyze MeSH and keywords of studies fitting your criteria and revise strategy
- Rerun search with revised strategy
- Run optimal search strategy
- Retrieve reports identified with optimal search strategy

Documenting search results and conclusions through prisma flow of information

ASSESSING RISK OF BIAS IN CLINICAL TRIALS:

RISK- bias in methods used in included studies

Bias in systematic review- bias in methods used in systematic review

Study Quality- it refers to the methods used to conduct a study (the way the study was actually done)

Elements of study quality that can be assessed by reading study report: internal validity, external validity, relevance, originality, ethics

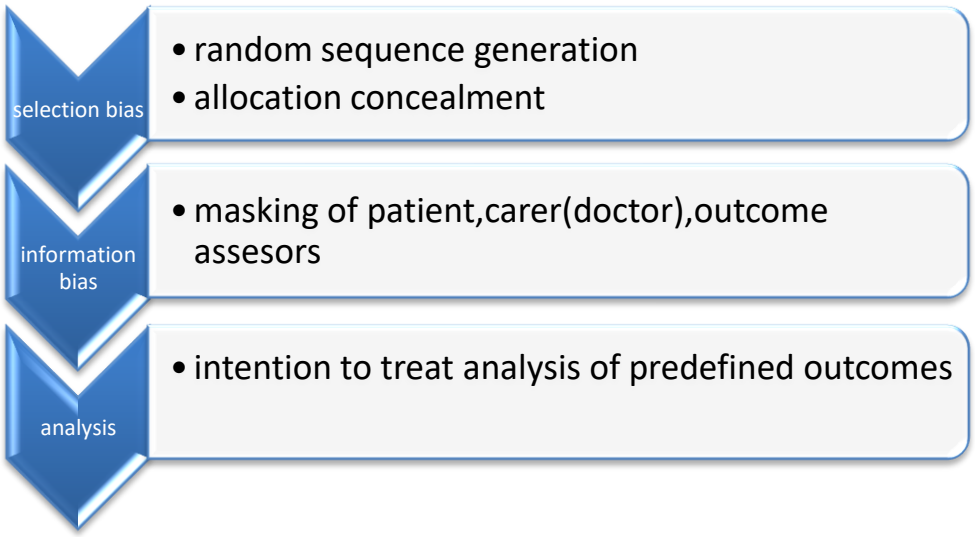
That cannot be assessed: protocol violations, quality of record keeping, quality of study procedures, degree to which report reflects the actual study, fabrication and falsification of details

So, for a quality systematic review, the include studies should be unbiased or minimally biased.

Three types of biases are observed most commonly in RCT.

1. Selection bias
2. Information bias
3. Analysis(avoiding bias in doing analysis)

SELECTION BIAS:



Random sequence generation:

It occurs at the start of trials before the allocation of participants. Determines a random order of assigning people into intervention and control groups. Accounts for known and unknown confounders. It prevents systematic differences between groups. It mainly helps in the prevention of selection bias.

Low risk bias in random sequence generation:

- Random numbers table
- Computer random number generator
- Stratified or block randomization
- Coin toss, shuffling cards or envelopes, throwing dice

High risk bias in random sequence generation:

- Quasi random- date of birth, day of visit, ID or record number, alternate allocation
- Non random- choice of clinician or patient, test results, availability

Allocation concealment:

It occurs at the start of trial during the allocation of participants. When a participant is recruited to a study, no one is able to predict which group the person will be allotted to. This ensures strict implementation of randomly generated sequence which prevents changing the order, prevents selecting to recruit.

Low risk of bias:

- Central allocation(web, phone, pharmacy)
- Sequentially numbered, sealed , opaque envelopes
- Sequentially numbered identical drug containers

High risk of bias:

- Random sequence known to staff in advance
- Envelopes or packaging without all safeguards
- Non random predictable sequence

INFORMATION BIAS

Masking or blinding of patients and personnel prevents information bias.

Low risk of bias:

- Masking, and unlikely that masking could have been broken
- No masking or incomplete masking, but outcome likely to be influenced

High risk of bias:

- No masking or incomplete masking, but outcome likely to be influenced

BIAS IN ANALYSIS

Occurs in situations of losses of follow up, non compliance, withdrawals, changes in the outcome measure. May also occur due to missing data.

DISPLAYING STUDY QUALITY IN SYSTEMATIC REVIEW:

Some of the ways quality/ heterogeneity is handled in analysis: risk of bias table, visual methods to assess, quality threshold (minimum sample size or number of events), perform sensitivity analysis(repeating analysis excluding studies with high risk studies), weight in regression equation

QUALITATIVE SYNTHESIS AND INTERPRETING RESULTS

- Qualitative synthesis: an assessment of body of evidence that goes beyond factual descriptions or tables. For example, details of how many studies assessed, reasons for exclusions, the range of study sizes etc., quantitative synthesis is not always a sensitive

step and is only good as the qualitative synthesis precedes it. A qualitative synthesis should describe how the body of the evidence agrees or contrasts with conventional wisdom. It should call attention to patient populations that have been inadequately examined and to those for whom outcomes differ. It should describe differences in designs and association of individual studies and how that may relate to differing findings in those studies. Involves numerous judgments

Relevance, uncertainty and legitimacy of evidence

Implications of missing evidence

Soundness of technical methods

Appropriateness of conducting meta analysis

- Synthesis must be appropriately balanced and driven by data

Purpose: to develop and convey a deeper understanding of how intervention might be working (or not), why true association exists, for whom and under what circumferences. To orient reader to clinical background like describe what happened to study participants over course of studies, critique the strengths and weaknesses of body of evidence, describe how the design and execution of individual studies effect their relevance to real world settings, describe how systematic reviews findings contrasts with conventional

ITEMS TO DESCIBE IN QUALITATIVE SYNTHESIS

- Clinical and methodological characteristics of included studies
- Strengths and limitations of included studies
- Relevance of studies
- Flaws and bias
- Relationships between study characteristics and their reported findings

Qualitative synthesis

- Describe- nature of evidence in literature
- Interpret- possible effect of many differences among studies
- Evaluate- strengths and weaknesses in evidence base
- Conclude- combinality ?

PLANNING META ANALYSIS AND STATISTICAL REVIEW

Systematic reviews contain analyses of the primary studies and primary studies include analyses of their participants

- Qualitative: structured summary, description, and discussion of studies characteristics that may affect the cumulative evidence
- Quantitative: involves statistical analysis(meta analysis)

A general framework for synthesis:

- What is the direction of effect (association)
- What is the size of the effect
- Is the effect consistent across studies
- What is the strength of effect for the studies

META ANALYSIS: it is an optional component of systematic review. It refers to the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrate the findings. Conventional Meta analysis focus on pair-wise comparisons of interventions (or exposure). Meta Analysis are done only when studies are comparable, homogenous.

Combining results in Meta analysis:

- Justification of combining results:
    - Studies are estimating – in whole or in part – a common effect
    - Studies are addressing the same fundamental biological/clinical/mechanistic question

Eg: each study represented by its point estimate and 95% confidence interval

Reasons to perform Meta analysis:

- Increase power and precision (detect narrow confidence interval, statistically significant or not)
- Quantify effect size and their uncertainty (reduce problems of interpretation due to sampling variations)
- Assess homogeneity or heterogeneity of results(quantify among study variation)
- Answer questions not posed by individual studies (factors that differ across studies comparative effectiveness of multiple interventions)
- Settle controversies arising from conflicting studies (generate new hypothesis)

Meta analysis can also be defined as the statistical analysis which combines the results of several independent studies considered by the analyst to be combinable. Each study will have that summary measure. Meta analysis estimates the overall measure effect as an average. In meta analysis, we consider weighted average to estimate overall measure effect.

Weighted averages:

- Each study is summarized by an estimate of effect(the result) Eg: risk ratio
- Overall measure of effect is a weighted average of results of individual studies
- Weighted averages reflect varying importance of trials
    . Desire ‘more weight’ if more information is needed (mainly sample size)

. ‘More information’ leads to ‘increased precision’

There are two types of models for Meta analysis

- Fixed effect model: under fixed effect model, we assume that all studies are identical and each individual study estimated a true common effect size which is same. True effect size is denoted by theta.
- Random effect model: here, we assume that there is a distribution of true effects.
  In fixed model effect, we have only one source of variance (within study variance). Whereas, in random effect model, there is variance between studies (between study variance)

KEY LEARNINGS FROM THE COURSE

- the steps in conducting a systematic review
- Develop an answerable question using the “Participants Interventions Comparisons Outcomes” (PICO) framework
- the process used to collect and extract data from reports of clinical trials
- methods to critically assess the risk of bias of clinical trials
- Describe and interpret the results of meta-analyses